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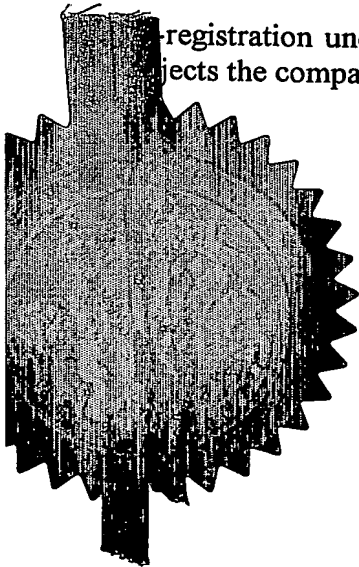
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SCH/DAB/PG4895

2. Patent application number

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0219305.0

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

United Kingdom

473587003

4. Title of the invention

Pyrimidine Derivatives

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

Patents ADP number (if you know it)

Corporate Intellectual Property

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980 Great West Road
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Claim(s) / 3 DM
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11.

We request the grant of a patent on the basis of this application

Signature  Date 16-Aug-02
S C Hockley

12. Name and daytime telephone number of person to contact in the United Kingdom

S C Hockley 01279 644355

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Notes

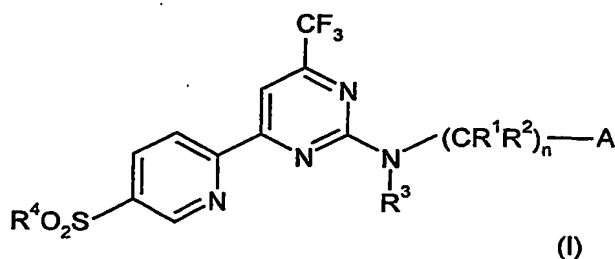
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PYRIMIDINE DERIVATIVES

This invention relates to pyrimidine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

5 The enzyme cyclooxygenase (COX) has recently been discovered to exist in two isoforms, COX-1 and COX-2. COX-1 corresponds to the originally identified constitutive enzyme while COX-2 is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. Prostaglandins generated by the action of COX have both physiological and pathological roles. It is generally believed that COX-1 is largely responsible for the important physiological functions such as maintenance of gastrointestinal integrity and renal blood flow. In contrast the inducible form, COX-2, is believed to be largely responsible for the pathological effects of prostaglandins where rapid induction of the enzyme occurs in response to such agents as inflammatory agents, hormones, growth factors and cytokines. A selective inhibitor of COX-2 would therefore have anti-inflammatory, anti-pyretic and analgesic properties, without the potential side effects associated with inhibition of COX-1. We have now found a novel group of compounds which are both potent and selective inhibitors of COX-2.

20 The invention thus provides a compound of formula (I)



and pharmaceutically acceptable salts thereof in which:

- R¹ and R² are independently selected from H or C₁₋₆alkyl;
 R³ is selected from the group consisting of H and C₁₋₆alkyl;
 25 R⁴ is selected from the group consisting of C₁₋₆alkyl, NH₂ and R⁶CONH;

A is C₅₋₇cycloalkyl or an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more R⁵;

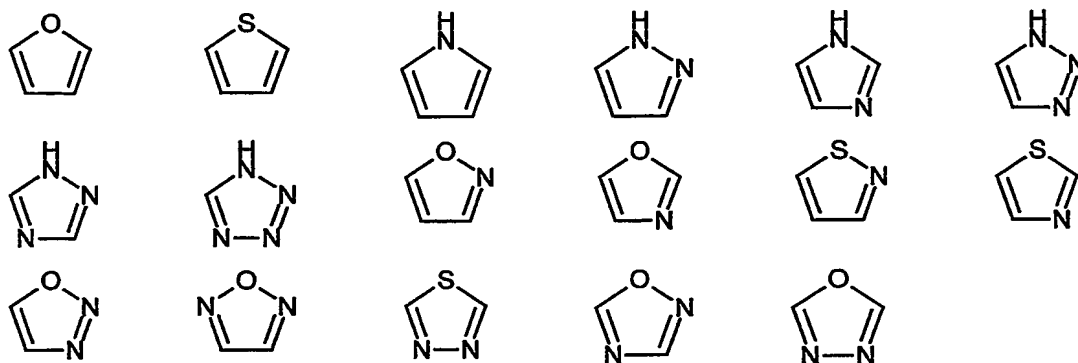
- 5 R⁵ is selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆alkyl substituted by one more fluorine atoms, C₁₋₆alkoxy, C₁₋₆alkoxy substituted by one or more F, NH₂SO₂ and C₁₋₆alkylSO₂;

- 10 R⁶ is selected from the group consisting of H, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkylOC₁₋₆alkyl, phenyl, HO₂CC₁₋₆alkyl, C₁₋₆alkylOCOC₁₋₆alkyl, C₁₋₆alkylOCO, H₂NC₁₋₆alkyl, C₁₋₆alkylOCONHC₁₋₆alkyl and C₁₋₆alkylCONHC₁₋₆alkyl; and n is 0 to 4.

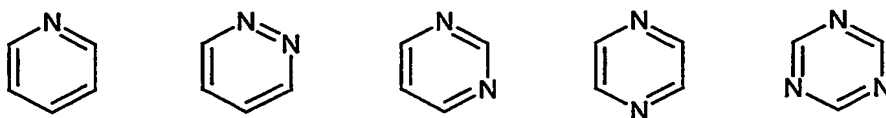
The term halogen is used to represent fluorine, chlorine, bromine or iodine.

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group.

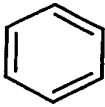
- 15 The term 5-membered heteroaryl means a heteroaryl selected from the following:



- 20 The term 6-membered heteroaryl means a heteroaryl selected from the following:



The term 6-membered aryl means:



5 It is to be understood that the present invention encompasses all isomers of the compounds of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Furthermore, it will be appreciated by those skilled in the art that when R^1 and R^2 in formula (I) are different the corresponding compounds contain at least one chiral centre, by virtue of the asymmetric carbon atom defined thereby, and that such compounds exist in the form of a pair of optical
10 isomers (i.e. enantiomers).

15 It will be appreciated that in some instances, compounds of the present invention may include a basic function such as an amino group as a substituent. Such basic functions may be used to form acid addition salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Such salts may be formed from inorganic and organic acids. Representative examples thereof include maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic,
20 itaconic, glycolic, p-aminobenzoic, glutamic, taurocholic acid, benzenesulfonic, p-toluenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

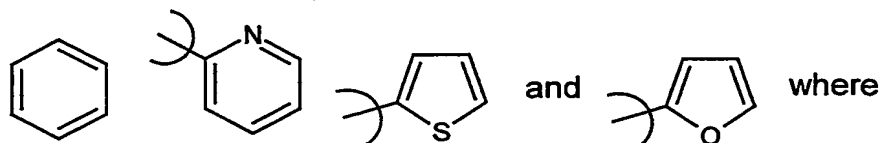
25 It will be appreciated that in some instances, compounds of the present invention may include a carboxy group as a substituent. Such carboxy groups may be used to form salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Preferred salts include alkali metal salts such as the sodium and potassium salts.

30 In one aspect of the invention R^1 and R^2 are independently selected from H or methyl. In another aspect R^1 and R^2 are both H.

In another aspect of the invention R^3 is H or methyl.

In another aspect of the invention R^4 is C_{1-3} alkyl (e.g. methyl).

In another aspect of the invention A is selected from the group consisting of C_{5-7} cycloalkyl or



- 5) defines the point of attachment of the ring
and A is unsubstituted or substituted by one or two R^5 .

In another aspect of the invention R^5 is selected from the group consisting of halogen (e.g. F), C_{1-3} alkyl (e.g. methyl), C_{1-3} alkyl substituted by one to three fluorine atoms (e.g. CF_3), and C_{1-3} alkoxy (e.g. methoxy).

- 10 In another aspect of the invention R^6 is selected from the group consisting of C_{1-6} alkyl (e.g. ethyl), phenyl and aminomethyl.

In another aspect of the invention n is 0 to 2 (e.g. 1).

It is to be understood that the invention covers all combinations of particular aspects of the invention as described hereinabove.

- 15 In a preferred aspect the invention provides the following compounds:
[4-(5-Methanesulfonyl-pyridin-2-yl)-6-trifluoromethyl-pyrimidin-2-yl]-methyl-(6-methyl-pyridin-2-ylmethyl)-amine,
Benzyl-[4-(5-methanesulfonyl-pyridin-2-yl)-6-trifluoromethyl-pyrimidin-2-yl]-amine,
20 Cyclohexyl-[4-(5-methanesulfonyl-pyridin-2-yl)-6-trifluoromethyl-pyrimidin-2-yl]-amine.

- 25 Since the compounds of the present invention, in particular compounds of formula (I), are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95%

pure (% are on a wt/wt basis). Impure preparations of the compound of formula (I) may be used for preparing the more pure forms used in pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever possible, the compounds of the present invention are available in crystalline form.

When some of the compounds of this invention are allowed to crystallise or are recrystallised from organic solvents, solvent of recrystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation. In addition, different crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all the polymorphic forms of the compounds of formula (I).

Compounds of the invention are potent and selective inhibitors of COX-2. This activity is illustrated by their ability to selectively inhibit COX-2 over COX-1.

In view of their selective COX-2 inhibitory activity, the compounds of the present invention are of interest for use in human and veterinary medicine, particularly in the treatment of the pain (both chronic and acute), fever and inflammation of a variety of conditions and diseases mediated by COX-2. Such conditions and diseases are well known in the art and include rheumatic fever; symptoms associated with influenza or other viral infections, such as the common cold; lower back and neck pain; headache; toothache; sprains and strains; myositis; sympathetically maintained pain; synovitis; arthritis, including rheumatoid arthritis; degenerative joint diseases, including osteoarthritis; gout and ankylosing spondylitis; tendinitis; bursitis; skin related conditions, such as psoriasis, eczema, burns and dermatitis; injuries, such as sports injuries and those arising from surgical and dental procedures.

The compounds of the invention are also useful for the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the

resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them.

5 Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific
~~lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy;~~
neuralgia, such as post-herpetic neuralgia and trigeminal neuralgia; and pain
10 resulting from physical trauma, amputation, cancer, toxins or chronic
inflammatory conditions. These conditions are difficult to treat and although
several drugs are known to have limited efficacy, complete pain control is rarely
achieved. The symptoms of neuropathic pain are incredibly heterogeneous and
are often described as spontaneous shooting and lancinating pain, or ongoing,
burning pain. In addition, there is pain associated with normally non-painful
15 sensations such as "pins and needles" (paraesthesias and dysesthesias),
increased sensitivity to touch (hyperesthesia), painful sensation following
innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity
to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain
sensation after removal of the stimulation (hyperpathia) or an absence of or
deficit in selective sensory pathways (hypoalgesia).

20 The compounds of the invention are also useful for the treatment of other
conditions mediated by COX-2.

For example, the compounds of the invention inhibit cellular and neoplastic
transformation and metastatic tumour growth and hence are useful in the
treatment of certain cancerous diseases, such as colonic cancer and prostate
25 cancer. The compounds of the invention are also useful in reducing the number
of adenomatous colorectal polyps and thus reduce the risk of developing colon
cancer. The compounds of the invention are also useful in the treatment of
cancer associated with overexpression of HER-2/neu, in particular breast
cancer.

30 Compounds of the invention also prevent neuronal injury by inhibiting the
generation of neuronal free radicals (and hence oxidative stress) and therefore
are of use in the treatment of stroke; epilepsy; and epileptic seizures (including
grand mal, petit mal, myoclonic epilepsy and partial seizures).

Compounds of the invention also inhibit prostanoid-induced smooth muscle contraction and hence are of use in the treatment of dysmenorrhoea and premature labour.

5 Compounds of the invention are also useful in the treatment of liver disease, such as inflammatory liver disease, for example chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury, primary biliary cirrhosis, autoimmune hepatitis, nonalcoholic steatohepatitis and liver transplant rejection.

10 Compounds of the invention inhibit inflammatory processes and therefore are of use in the treatment of asthma, allergic rhinitis and respiratory distress syndrome; gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis; and the inflammation in such diseases as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, scleroderma, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, 15 Bechet's syndrome, polymyositis, gingivitis, conjunctivitis and myocardial ischemia.

Compounds of the invention are also useful in the treatment of ophthalmic diseases such as retinitis, retinopathies, uveitis and of acute injury to the eye tissue.

20 Compounds of the invention are also useful for the treatment of cognitive disorders such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease and Creutzfeldt-Jakob disease), and vascular dementia (including multi-infarct dementia), as well as dementia associated with intracranial space 25 occupying lesions, trauma, infections and related conditions (including HIV infection), metabolism, toxins, anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

30 Compounds of the invention are also useful in the treatment of disorders ameliorated by a gastroprokinetic agent. Disorders ameliorated by gastroprokinetic agents include ileus, for example post-operative ileus and ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); gastroparesis, such as diabetic gastroparesis; and other functional bowel

disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP).

According to a further aspect of the invention, we provide a compound of formula (I) for use in human or veterinary medicine.

5 ~~According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by COX-2 which comprises administering to said subject an effective amount of a compound of formula (I).~~

10 According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from an inflammatory disorder, which method comprises administering to said subject an effective amount of a compound of formula (I).

15 According to another aspect of the invention, we provide the use of a compound of formula (I) for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by COX-2.

According to another aspect of the invention, we provide the use of a compound of formula (I) for the manufacture of a therapeutic agent for the treatment of an inflammatory disorder.

20 It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

25 It will be appreciated that the compounds of the invention may advantageously be used in conjunction with one or more other therapeutic agents. Examples of suitable agents for adjunctive therapy include a 5HT₁ agonist, such as a triptan (e.g. sumatriptan or naratriptan); an adenosine A₁ agonist; an EP ligand; an NMDA modulator, such as a glycine antagonist; a sodium channel blocker (e.g. lamotrigine); a substance P antagonist (e.g. an NK₁ antagonist); a cannabinoid; acetaminophen or phenacetin; a 5-lipoxygenase inhibitor; a leukotriene receptor antagonist; a DMARD (e.g. methotrexate); gabapentin and related compounds; a 30 tricyclic antidepressant (e.g. amitryptilline); a neurone stabilising antiepileptic drug; a mono-aminergic uptake inhibitor (e.g. venlafaxine); a matrix metalloproteinase inhibitor; a nitric oxide synthase (NOS) inhibitor, such as an

5 INOS or an nNOS inhibitor; an inhibitor of the release, or action, of tumour
necrosis factor α ; an antibody therapy, such as a monoclonal antibody therapy;
an antiviral agent, such as a nucleoside inhibitor (e.g. lamivudine) or an immune
system modulator (e.g. interferon); an opioid analgesic; a local anaesthetic; a
10 stimulant, including caffeine; an H₂-antagonist (e.g. ranitidine); a proton pump
inhibitor (e.g. omeprazole); an antacid (e.g. aluminium or magnesium hydroxide);
an antiflatulent (e.g. simethicone); a decongestant (e.g. phenylephrine,
phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine,
naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine); an
15 antitussive (e.g. codeine, hydrocodone, carmiphen, carbetapentane, or
dextramethorphan); a diuretic; or a sedating or non-sedating antihistamine. It is
to be understood that the present invention covers the use of a compound of
formula (I) in combination with one or more other therapeutic agents.

15 The compounds of formula (I) are conveniently administered in the form of
pharmaceutical compositions. Thus, in another aspect of the invention, we
provide a pharmaceutical composition comprising a compound of formula (I)
adapted for use in human or veterinary medicine. Such compositions may
conveniently be presented for use in conventional manner in admixture with one
or more physiologically acceptable carriers or excipients.

20 The compounds of formula (I) may be formulated for administration in any
suitable manner. They may, for example, be formulated for topical
administration or administration by inhalation or, more preferably, for oral,
transdermal or parenteral administration. The pharmaceutical composition may
be in a form such that it can effect controlled release of the compounds of
25 formula (I).

For oral administration, the pharmaceutical composition may take the form of, for
example, tablets (including sub-lingual tablets), capsules, powders, solutions,
syrups or suspensions prepared by conventional means with acceptable
excipients.

30 For transdermal administration, the pharmaceutical composition may be given in
the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as
an injection or a continuous infusion (e.g. intravenously, intravascularly or

subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or
5 as a multidose presentation preferably with an added preservative.

Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

10 The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

15 As stated above, the compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) together with a further therapeutic agent.

20 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical
25 formulations.

When a compound of formula (I) is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

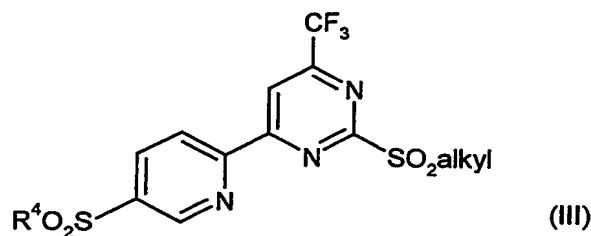
30 A proposed daily dosage of a compound of formula (I) for the treatment of man is 0.01mg/kg to 500mg/kg, such as 0.05mg/kg to 100mg/kg, e.g. 0.1mg/kg to 50mg/kg, which may be conveniently administered in 1 to 4 doses. The precise

dose employed will depend on the age and condition of the patient and on the route of administration. Thus, for example, a daily dose of 0.25mg/kg to 10mg/kg may be suitable for systemic administration.

5 Compounds of formula (I) may be prepared by any method known in the art for the preparation of compounds of analogous structure.

Compounds of formula (I) may be prepared by a process which comprises:

reacting an amine $\text{HNR}^3(\text{CR}^1\text{R}^2)_n\text{A}$ of formula (II) or a protected derivative thereof with a compound of formula (III)



10 and thereafter and if necessary, interconverting a compound of formula (I) into another compound of formula (I); and/or deprotecting a protected derivative of compound of formula (I).

15 The overall synthesis of a compound of formula (I) is shown in Scheme 1 below in which, R^1 , R^2 and R^3 are as defined in formula (I) above unless otherwise stated, R^4 is C_{1-6} alkyl; THF is tetrahydrofuran; MTBE is methyl t-butyl ether; and alkyl is a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group.

20 Referring to Scheme 1, when $\text{X}=\text{NR}^2$, compounds of formula (I) may be prepared via the treatment of compounds of formula (III) with an amine of formula (II). This is conveniently carried out in a solvent, such as a nitrile (e.g. methylnitrile) and at elevated temperature (e.g from about 50°C to reflux). An excess of the amine may be used in place of the solvent.

25 Alternatively, the treatment of compounds of formula (III) with an amine of formula (II) is conveniently carried out in a solvent, such as a tertiary amine (e.g. NMP) and at elevated temperature (e.g. from 120°C to 250°C) and with or without microwave irradiation.

Conveniently the oxidation shown in Scheme 1 is effected using a monopersulfate compound, such as potassium peroxymonosulfate (known as OxoneTM) and the reaction is carried out in a solvent, such as an aqueous alcohol, (e.g. aqueous methanol), and at between -78°C and ambient temperature.

Alternatively, the oxidation shown in Scheme 1 may be effected using hydrogen peroxide in the presence of catalytic sodium tungstate dihydrate. The reaction may be carried out in a solvent such as acetic acid and at between ambient temperature and reflux (e.g. 50°C).

10 Referring to Scheme 1, the cyclisation of diones of formula (VI) to give the corresponding pyrimidines of formula (IV) is conveniently carried out employing a thioronium salt such as a 2-methyl-2-thiopseudourea sulfate and under reflux.

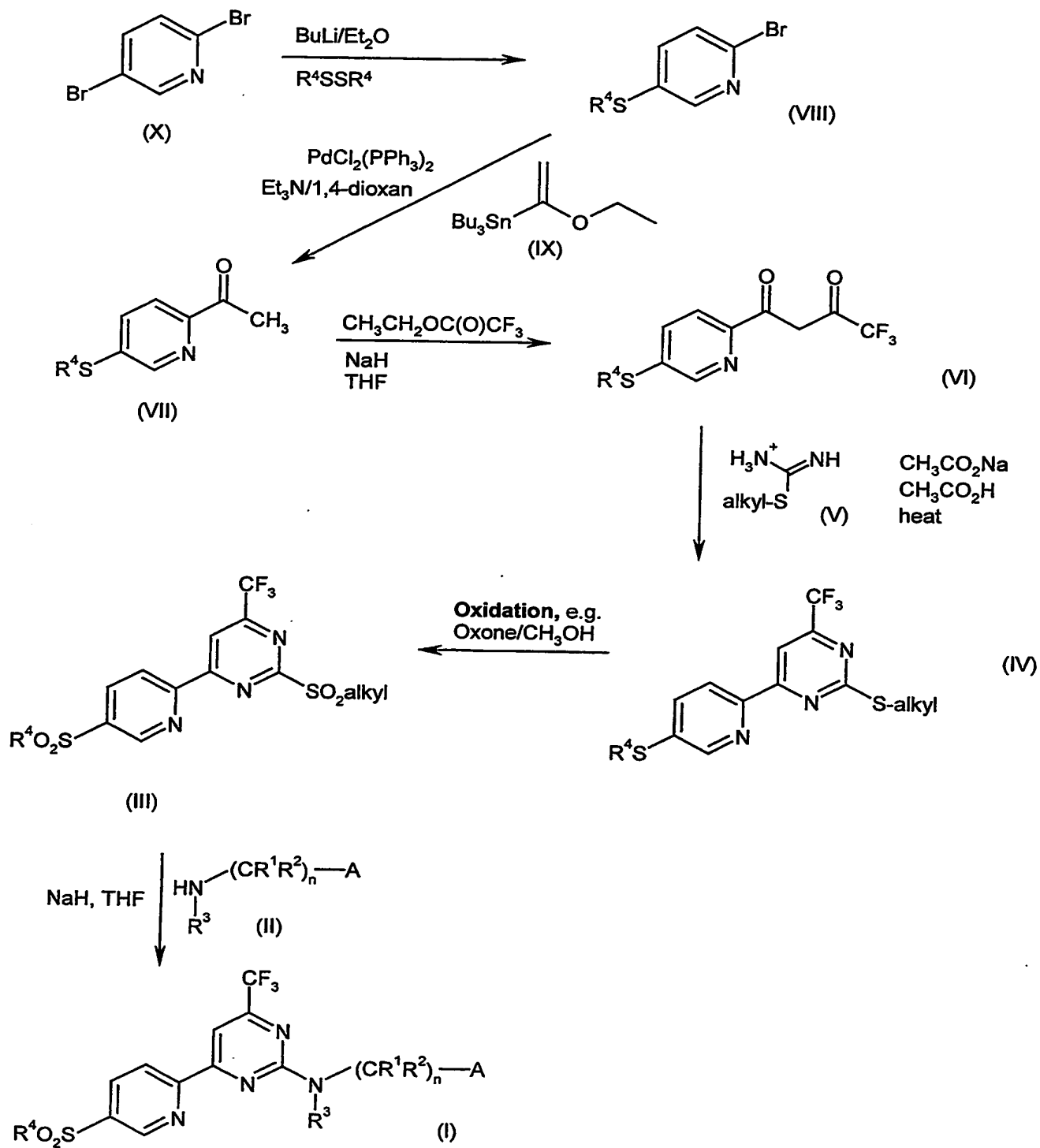
15 Compounds of formula (VI) may be readily prepared from acetophenones of formula (VII) via treatment with ethyl trifluoroacetate (Aldrich) in the presence of sodium hydride. The reaction is conveniently carried out in a suitable solvent such as tetrahydrofuran at a temperature between 0°C and reflux.

20 Acylation of compounds of formula (VIII) to give compounds of formula (VII) can be conveniently achieved by treatment with the compound of formula (IX) in the presence of triethylamine and a catalytic quantity of dichlorobis(triphenylphosphine) palladium (II). The reaction is suitably performed in a solvent such as 1,4-dioxan at a temperature between ambient and reflux.

25 Alternatively, the acylation of compounds of formula (VIII) to give compounds of formula (VII) can be achieved via the treatment of (VIII) with excess *tert*-butyllithium in THF at low temperature, such as -78°C, followed by the addition of a suitable acylating agent such as dimethyl acetamide or N-methoxy-N-methyl acetamide.

30 Preparation of compounds of formula (VIII) may conveniently be achieved via treatment of compounds of formula (X) with butyllithium at low temperature, such as -78°C, followed by the addition of the appropriate disulfide. The reaction is conveniently carried out in a suitable solvent such as diethyl ether at a temperature between -78°C and ambient temperature.

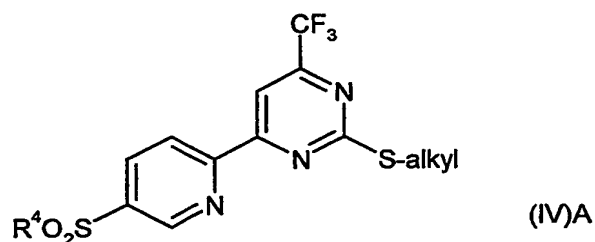
Scheme 1



It will be appreciated by those skilled in the art that certain of the procedures described in Scheme 1 for the preparation of compounds of formula (I) or intermediates thereto may not be applicable to some of the possible substituents.

5 It will be further appreciated by those skilled in the art that it may be necessary or desirable to carry out the transformations described in Scheme 1 in a different order from that described, or to modify one or more of the transformations, to provide the desired compound of formula (I).

10 In one variation of Scheme 1, compounds of formula (III) wherein R^4 is C_{1-6} alkyl may be prepared by oxidising a compound of formula (IV)A:



15 under oxidation conditions described hereinabove. Compounds of formula (IV)A may be prepared according to the general procedures of Scheme 1 by employing sulphonyl derivatives in place of the corresponding sulfide compounds of formulae (VI), (VII) and (VIII). In this instance the sulfonyl derivative of compound of formula (VIII) may be prepared via oxidation of (VIII) using standard techniques, such as those hereinbefore described.

20 It will be appreciated by those skilled in the art that compounds of formula (I) may be prepared by interconversion, utilising other compounds of formula (I) as precursors. Suitable interconversions, such as alkylations, are well known to those skilled in the art and are described in many standard organic chemistry texts, such as 'Advanced Organic Chemistry' by Jerry March, fourth edition (Wiley, 1992), incorporated herein by reference. For example, compounds of formula (I) wherein R^3 is C_{1-6} alkyl may be prepared by alkylating the
25 corresponding compound of formula (I) wherein R^3 is H.

Acylation of compounds of formula (I) wherein R^4 is NH_2 , to provide compounds of formula (I) wherein R^4 is $NHCOR^6$, may be carried out by conventional means, for example by employing conventional acylating agents such as those

described in 'Advanced Organic Chemistry', pp 417-424, incorporated herein by reference.

5 As will be appreciated by those skilled in the art it may be necessary or desirable at any stage in the synthesis of compounds of formula (I) to protect one or more sensitive groups in the molecule so as to prevent undesirable side reactions. The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See, for example, those described in 'Protective Groups in Organic Synthesis' by Theodora W Green and Peter G M Wuts, second edition, (John Wiley and Sons, 1991), incorporated herein by
10 reference, which also describes methods for the removal of such groups.

Amines of formula (II) are either known compounds or may be prepared by literature methods, such as those described in 'Comprehensive Organic Transformations: a guide to functional group preparations' by Richard Larock (VCH, 1989), incorporated herein by reference.

15 Thionium salts of formula (V) are either known compounds or may be prepared by literature methods, such as those described in A H Owens *et al*, Eur J Med Chem, 1988, 23(3), 295-300, incorporated herein by reference

Compounds (IX) and (X) are commercially available.

20 Certain intermediates described above are novel compounds, and it is to be understood that all novel intermediates herein form further aspects of the present invention. Compounds of formulae (III) and (IV) are key intermediates and represent a particular aspect of the present invention.

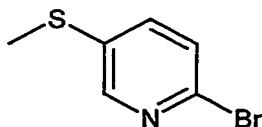
Solvates (e.g. hydrates) of a compound of the invention may be formed during the work-up procedure of one of the aforementioned process steps.

25 The Intermediates and Examples that follow illustrate the invention but do not limit the invention in any way. All temperatures are in °C. Flash column chromatography was carried out using Merck 9385 silica. Solid Phase Extraction (SPE) chromatography was carried out using Varian Mega Bond Elut (Si) cartridges (Anachem) under 15mmHg vacuum. Thin layer
30 chromatography (Tlc) was carried out on silica plates. In addition to those already defined, the following abbreviations are used: Me, methyl; Ac, acyl; DMSO, dimethylsulphoxide; TFA, trifluoroacetic acid; DME, dimethoxyethane;

DCM, dichloromethane; NMP, N- methyl pyrrolidone; and MTBE, methyl t-butyl ether.

Intermediate 1

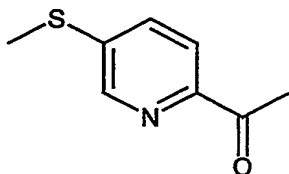
5 2-Bromo 5-methylsulfanyl pyridine



10 A stirring suspension of 2,5-dibromopyridine (10g, 0.042mol) in anhydrous diethyl ether (240mL) was cooled to -78°C under nitrogen before the dropwise addition of n-butyl lithium (1.6M in hexanes, 0.044mol, 27.5mL). The reaction was stirred at -78°C for 4 hours before the dropwise addition of methyl disulphide (0.044mol, 3.91mL). The reaction was allowed to warm to 22°C and stirred for a further 18 hours. The reaction was quenched with water (100mL) and the aqueous and organic layers partitioned. The aqueous layer was
15 extracted with diethyl ether (x3). The extracts were combined with the organic layer, washed with brine, dried (MgSO_4) and the solvent removed. The crude product was purified by crystallisation from diethyl ether at -20°C to afford the title compound as a white solid: $^1\text{H NMR}$ (CDCl_3) - δ 2.50 (s, 3H), 7.38 (dd, 1H),
20 7.42 (dd, 1H), 8.23 (d, 1H).

Intermediate 2

1-(5-Methylsulfanyl-pyridin-2-yl)-ethanone

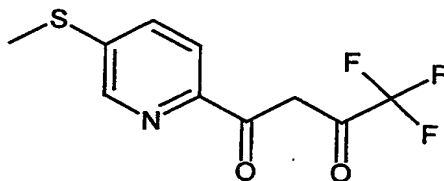


25 To a stirring solution of 2-bromo 5-methylsulfanyl pyridine (3.05g 14.9mmol), triethylamine (2.10mL, 14.9mmol) and (1-ethoxyvinyl) tributyl tin (10.1mL, 29.8mmol) in anhydrous 1,4-dioxane (100mL), was added dichlorobis(triphenylphosphine) palladium (II) (5mol%, 0.524g) and the reaction heated to reflux under nitrogen for 18 hours. After cooling,

dichlorobis(triphenylphosphine) palladium (II) was added and the reaction heated under nitrogen for a further 18 hours. The reaction was allowed to cool and the reaction mixture partitioned between saturated aqueous potassium fluoride solution (250mL) and diethyl ether (250mL). The ether layer was separated and 2N hydrochloric acid (250mL) added. The acid layer was separated and sodium carbonate added portionwise until the solution reached pH 8. The solution was extracted with dichloromethane (3 x 200mL). The organic extracts were combined and the solvent removed. The residue was partitioned between cyclohexane (60ml) and acetonitrile (60mL). The acetonitrile layer was separated and the solvent removed to yield a brown solid. The crude product was purified by flash column chromatography (cyclohexane:ethyl acetate, 95:5) to afford the title compound as a white solid: $^1\text{H NMR}$ (CDCl_3) - δ 2.56 (s, 3H), 2.69 (s, 3H), 7.60 (dd, 1H), 7.96 (d, 1H), 8.49 (d, 1H).

Intermediate 3

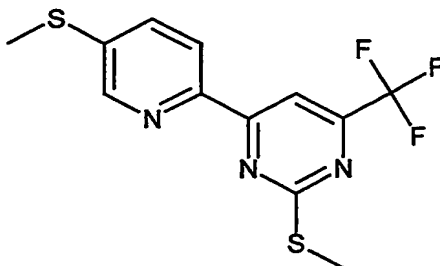
4,4,4-Trifluoro-1-(5-methylsulfanyl-pyridin-2-yl)-butane-1,3-dione



A stirring solution of sodium hydride (0.253g, 6.31mmol) in anhydrous tetrahydrofuran (20mL) was cooled under nitrogen to 0°C before the addition of 1-(5-methylsulfanyl-pyridin-2-yl)-ethanone (0.880g, 5.26mmol) in anhydrous tetrahydrofuran (20mL). The reaction was then heated to reflux and stirred under nitrogen for 17 hours. The solvent was removed and the residue partitioned between saturated aqueous ammonium chloride (10mL) and dichloromethane (10mL). The aqueous layer was separated and extracted with DCM (x3). The organic layers were combined, dried and the solvent removed to yield the title compound: MS m/z 264 (M+1).

Intermediate 4

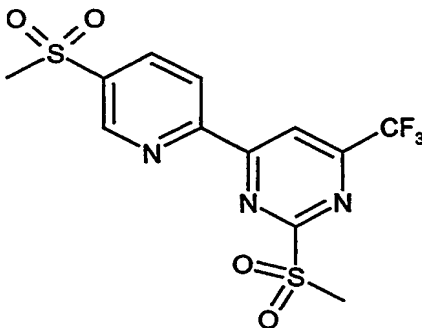
2-Methylsulfanyl-4-(5-methylsulfanyl-pyridin-2-yl)-6-trifluoromethyl-pyrimidine



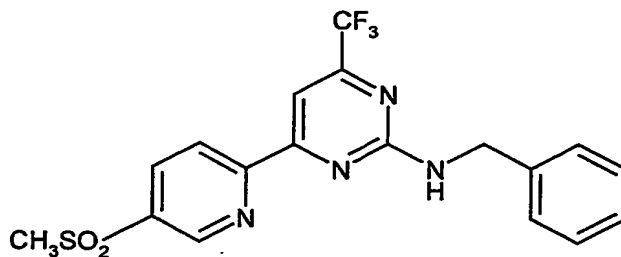
To a solution of 4,4,4-trifluoro-1-(5-methylsulfanyl-pyridin-2-yl)-butane-1,3-dione (0.600g, 2.28mmol) in glacial acetic acid (6mL) was added 2-methyl 2-thiopseudourea sulphate (0.761g, 2.74mmol) and sodium acetate (0.224g, 2.74mmol). The reaction was heated to 120°C under nitrogen for 21 hours. The reaction was allowed to cool before the addition of water (10mL), leading to precipitation of a solid. The reaction mixture was poured onto water (10mL) and stirred for 15 minutes at 22°C. The precipitate was filtered from the aqueous solution, washed with water, and dried *in vacuo* to yield the title compound as a grey solid: MS m/z 317 (M+1).

Intermediate 5

2-Methanesulfonyl-4-(5-methanesulfonyl-pyridin-2-yl)-6-trifluoromethyl-pyrimidine



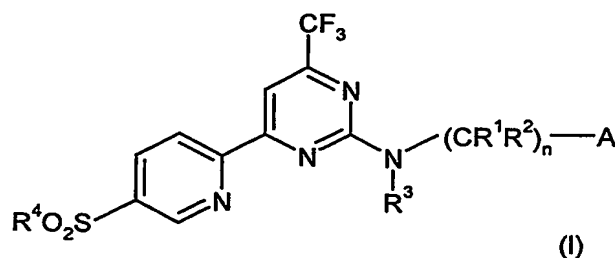
To a stirring solution of 2-methylsulfanyl-4-(5-methylsulfanyl-pyridin-2-yl)-6-trifluoromethyl-pyrimidine (0.617g, 1.94 mmol) in methanol (50mL) was added a solution of oxone (4.89g, 7.95mmol) in water (50mL). The suspension was stirred at 22°C for 19 hours. Methanol was removed *in vacuo* and the aqueous suspension extracted with ethyl acetate (3 x 50mL). The organic extracts were combined, dried (MgSO₄) and the solvents removed *in vacuo* to yield the title compound as a white solid. MS m/z 382 (M+1).

Example 1Benzyl-[4-(5-methanesulfonyl-pyridin-2-yl)-6-methyl-pyrimidin-2-yl-amine

To a solution of 2-methanesulfonyl-4-(5-methanesulfonyl-pyridin-2-yl)-6-
 5 trifluoromethyl-pyrimidine (30mg, 0.0787mmol) in anhydrous N-methyl
 pyrrolidinone (1.5mL) was added benzylamine (0.157mmol, 17 μ L). The reaction
 was stirred at 22°C for 17 hours. The solvent was removed from the reaction
 (Genevac vacuum centrifuge) and the residue purified using a 1g silica solid
 10 phase extraction cartridge (gradient elution - dichloromethane:cyclohexane 1:1
 to dichloromethane) to yield the title compound as a cream coloured solid: LC-
 MS retention time : 3.68 min. MS m/z 409 (M+1)

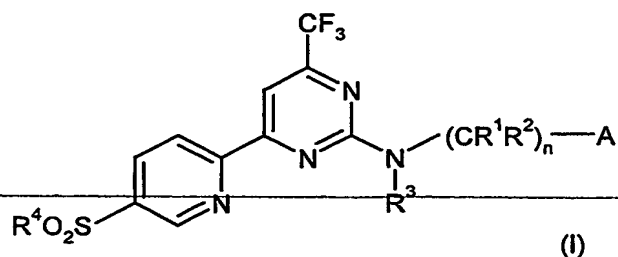
Examples 2 to 13

- 15 • Examples 2 to 13, as shown in Table 1 that follows, were prepared in the
 manner described for Example 1.

Table 1

Ex	A	R ¹	R ²	n	R ³	R ⁴	MS	
2	pyridin-2-yl	H	H	1	H	CH ₃	MH+	410
3	6-methyl-pyridin-2-yl	H	H	1	CH ₃	CH ₃	MH+	438
4	5-methyl-furan-2-yl	H	H	1	H	CH ₃	MH+	413
5	cyclohexyl			0	H	CH ₃	MH+	401

Table 1



Ex	A	R ¹	R ²	n	R ³	R ⁴	MS
6	cyclohexyl			0	CH ₃	CH ₃	MH+ 415
7	furan-2-yl	H	H	1	H	CH ₃	MH+ 399
8	thiophen-2-yl	H	H	1	H	CH ₃	MH+ 415
9	furan-2-yl	H	H	1	CH ₃	CH ₃	MH+ 413
10	4-chlorophenyl	H	H	1	H	CH ₃	MH+ 444
11	cyclopentyl			0	H	CH ₃	MH+ 387
12	phenyl	H	H	1	CH ₃	CH ₃	MH+ 423
13	4-methylphenyl	H	H	1	H	CH ₃	MH+ 423

Biological Data

Microsomal Assay

5 Inhibitory activity against microsomal h-COX2 was assessed against a microsomal preparation from baculovirus infected SF9 cells. An aliquot of microsomal preparation was thawed slowly on ice and a 1/40,000 dilution prepared from it into the assay buffer (sterile water, degassed with argon containing 100mM HEPES (pH 7.4), 10mM EDTA (pH7.4), 1mM phenol, 1mM reduced glutathione, 20mg/ml gelatin and 0.001mM Hematin). Once diluted the enzyme solution was then sonicated for 5 seconds (Branson sonicator, setting 4, 1cm tip) to ensure a homogeneous suspension. 155μl enzyme solution was then added to each well of a 96-well microtitre plate containing either 5μl test compound (40x required test concentration) or 5μl DMSO for controls. Plates were then mixed and incubated at room temperature for 1 hour. Following the incubation period, 40μl of 0.5μM arachidonic acid was added to each well to give

10

15

5 a final concentration of 0.1 μ M. Plates were then mixed and incubated for exactly 10 minutes (room temperature) prior to addition of 25 μ l 1M HCl (hydrochloric acid) to each well to stop the reaction. 25 μ l of 1M NaOH (sodium hydroxide) was then added to each well to neutralise the solution prior to determination of PGE₂ levels by enzyme immunoassay (EIA).

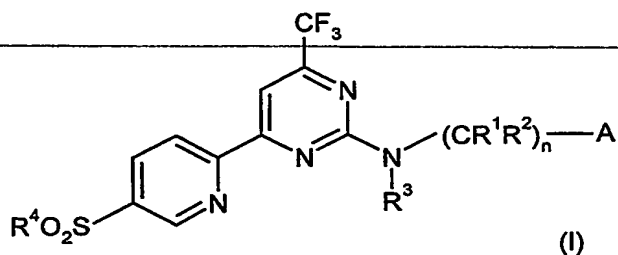
The following IC₅₀ values for inhibition of COX-2 and COX-1 were obtained from the microsomal assay for compounds of the invention:

Example No.	COX-2: IC ₅₀ (μ M)	COX-1: IC ₅₀ (μ M)
1	0.051	23.1
2	0.542	nt
3	0.005	67.1
4	0.218	>100
5	0.019	>100
6	0.077	26.3
7	0.748	46.8
8	0.04	nt
9	0.072	>100
10	0.354	90.2
11	0.433	>96.1
12	0.001	>100
13	0.193	>100

10 The application of which this description and these claims form a part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features relating to the invention described herein. They may take the form of a product, process or use claims and may include, by way of example and without limitation the claims that follow.

CLAIMS

1. A compound of formula (I)



- 5 and pharmaceutically acceptable salts thereof in which:

R^1 and R^2 are independently selected from H or C_{1-6} alkyl;

R^3 is selected from the group consisting of H and C_{1-6} alkyl;

R^4 is selected from the group consisting of C_{1-6} alkyl, NH_2 and R^6CONH ;

- 10 A is C_{5-7} cycloalkyl or an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more R^5 ;

R^5 is selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkyl substituted by one more fluorine atoms, C_{1-6} alkoxy, C_{1-6} alkoxy substituted by one or more F, NH_2SO_2 and $C_{1-6}alkylSO_2$;

- 15 R^6 is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkoxy, $C_{1-6}alkylOC_{1-6}alkyl$, phenyl, $HO_2CC_{1-6}alkyl$, $C_{1-6}alkylOCOC_{1-6}alkyl$, $C_{1-6}alkylOCO$, $H_2NC_{1-6}alkyl$, $C_{1-6}alkylIOCONHC_{1-6}alkyl$ and $C_{1-6}alkylICONHC_{1-6}alkyl$; and
n is 0 to 4.

20

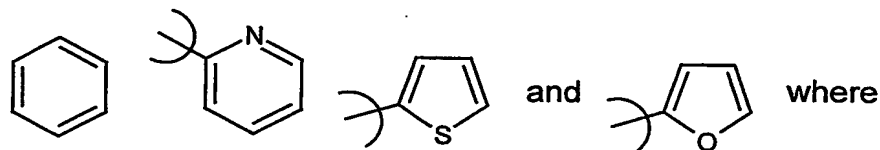
2. A compound according to claim 1 wherein R^1 and R^2 are independently selected from H or methyl.

3. A compound according to claim 1 or 2 wherein R^3 is H or methyl.

25

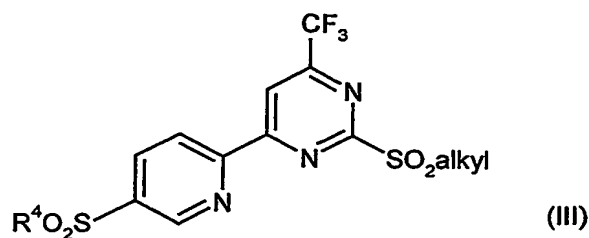
4. A compound according to any of claims 1 to 3 wherein R^4 is C_{1-3} alkyl.

5. A compound according to any of claims 1 to 4 wherein A is selected from the group consisting of C₅₋₇cycloalkyl or



) defines the point of attachment of the ring
and A is unsubstituted or substituted by one or two R⁵.

- 5
6. A compound according to any of claims 1 to 5 wherein R⁵ is selected from the group consisting of halogen, C₁₋₃alkyl, C₁₋₃alkyl substituted by one to three fluorine atoms, and C₁₋₃alkoxy.
- 10
7. A compound according to any of claims 1 to 6 wherein R⁶ is selected from the group consisting of C₁₋₆alkyl (e.g. ethyl), phenyl and aminomethyl.
8. A compound according to any of claims 1 to 7 wherein n is 0 to 2.
- 15
9. A compound as defined in claim 1 and as described in examples 1 to 13.
10. A process for the preparation of compounds of formula (I) as defined in any of claims 1 to 9 which comprises:
- 20
- (A) reacting an amine HNR³(CR¹R²)_nA of formula (II) or a protected derivative thereof with a compound of formula (III)



and thereafter and if necessary,

(B) interconverting a compound of formula (I) into another compound of formula (I); and/or

(C) deprotecting a protected derivative of compound of formula (I).

11. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 9 in admixture with one or more physiologically acceptable carriers or excipients.

5 ~~12. A compound of formula (I) as defined in any one of claims 1 to 9 for use in human or veterinary medicine.~~

10 13. A method of treating a human or animal subject suffering from a condition which is mediated by COX-2 which comprises administering to said subject an effective amount of a compound of formula (I) as defined in any one of claims 1 to 9.

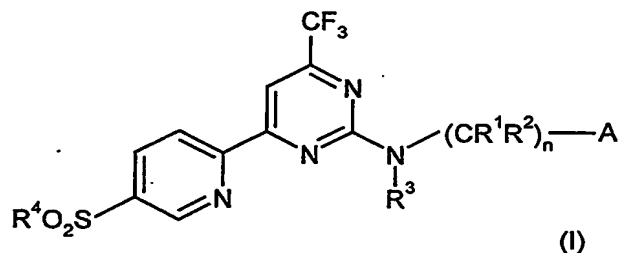
14. A method of treating a human or animal subject suffering from an inflammatory disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) as defined in any one of claims 1 to 9.

15 15. The use of a compound of formula (I) as defined in any one of claims 1 to 9 for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by COX-2.

20 16. The use of a compound of formula (I) as defined in any one of claims 1 to 9 for the manufacture of a therapeutic agent for the treatment of an inflammatory disorder.

Abstract

The invention provides the compounds of formula (I)



5 and pharmaceutically acceptable salts thereof in which:

R¹ and R² are independently selected from H or C₁₋₆alkyl;

R³ is selected from the group consisting of H and C₁₋₆alkyl;

R⁴ is selected from the group consisting of C₁₋₆alkyl, NH₂ and R⁶CONH;

10 A is C₅₋₇cycloalkyl or an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more R⁵;

R⁵ is selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆alkyl substituted by one more fluorine atoms, C₁₋₆alkoxy, C₁₋₆alkoxy substituted by one or more F, NH₂SO₂ and C₁₋₆alkylSO₂;

15 R⁶ is selected from the group consisting of H, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkylOC₁₋₆alkyl, phenyl, HO₂CC₁₋₆alkyl, C₁₋₆alkylOCOC₁₋₆alkyl, C₁₋₆alkylOCO, H₂NC₁₋₆alkyl, C₁₋₆alkylOCONHC₁₋₆alkyl and C₁₋₆alkylCONHC₁₋₆alkyl; and n is 0 to 4.

20 Compounds of formula (I) are potent and selective inhibitors of COX-2 and are of use in the treatment of the pain, fever and inflammation of a variety of conditions and diseases.